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Treatment of Acute Tuberculosis

Juan Torres-Gost, M.D.

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There was, until quite recently, no specific treatment for acute tuberculosis. On the treatment of chronic cavitary tuberculosis, however, there was abundant knowledge and a copious literature; including pneumothorax and pneumoperitoneum, surgery undoubtedly achieved some brilliant successes. Today we are better able to treat the acute forms, and in a great many cases, they can be prevented from developing into the chronic cavitary form.

Tuberculous meningitis. The present observations are based on the author's experience with over 250 cases of this disease. The spinal route is preferred for the administration of isoniazid, combined with oral and intramuscular routes for streptomycin, for the following reasons: (1) progress of patients is more rapid and freer of complications, as shown in 20 patients treated with oral isoniazid only, compared with a larger group that received spinal isoniazid; (2) rapid disappearance, in three to ten days, of the tubercle bacilli from the cerebrospinal fluid;* (3) no intrathecal adhesions are formed (the most serious complication of tuberculous meningitis). These are sometimes found when the oral route is used exclusively; (4) heavy concentration of isoniazid in the C.S.F. for several hours is not only harmless but quite beneficial; (5) patients treated orally require lumbar punctures to relieve headaches; the author sees no reason why 3 cc. of a totally harmless substance should not be injected where 15 or 20 cc. of C.S.F. have been withdrawn.† No sequelae of importance were observed except for some paresis of the limbs which disappeared during convalescence.

Our classification into mild forms, medium and grave forms continues to be clearly defined, being determined on the basis of fever charts. Relapses have practically

* One case treated orally showed bacilli in the C.S.F. two months later.

† Cf. Lancet, p. 693 (Oct. 3) 1953; Deutsche med. Wchnschr., p. 1708 (Dec. 4) 1953.

disappeared since complementary treatments and intermediate treatment with conteben.*

The practical results in the first 100 cases in which tuberculous meningitis was 18 months or more advanced, after treatment of the acute phase, were as follows: 6 patients died in the hospital—94 were discharged as cured. Two died later: one following laparotomy in connection with a suspected gastric ulcer, the other of an undetermined condition—probably septicemia; neither of these patients showed evidence of meningitis; a total of 92 patients are still alive, healthy, and free of any sequelae. In all but one case, the C.S.F. is completely normal; the exception shows slight alterations were found, which in no way interfere with the patient's regular office work. All patients were subjected to intelligence tests and showed no mental alterations.

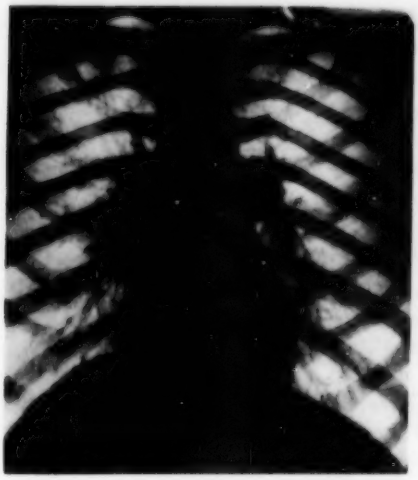
Therapeutic dosages were the following: First three months (acute phase): streptomycin intramuscular: children under 2 years—0.2 to 0.3 Gm. daily; very serious cases, up to 0.5 Gm.; 2 to 10 years—0.5 Gm. daily in a single dose; 10 to 15 years—1 Gm. daily in a single dose for 10 days, thereafter 0.5 Gm. daily until afebrile; adults—1 Gm. daily until afebrile. Isoniazid, oral: children under 2 years—150 mg., daily; 2 to 10 years—200 mg., daily; 10 to 15 years—300 mg., daily; adults—400 to 600 mg., daily. Isoniazid, intrathecal: children under 2 years—10 mg., daily; 2 to 10 years—20 to 30 mg., daily, according to gravity of the case; 10 to 15 years and adults—30 mg., daily. In very serious cases the dose is increased 5 mg. at a time up to a maximum of 50 mg.

This dosage scheme is subject to modification, according to the meningitis picture or to the gravity of the extrameningeal lesions. In the several thousands of intrathecal injections the author has made, there were no accidents. With practice, this route is no more difficult to use than the intravenous one. In this first course of treatment, the patients receive 30 to 60 Gm. streptomycin, 20 to 40 Gm. isoniazid orally and 45 intrathecal injections—30 in the first month and 15 in the second.

In the second three month period, the following treatment is given at home, in addition to rest: Children, two 0.025 Gm. conteben pills daily; adults, three 0.05 Gm. conteben pills daily, if tolerated—at the slightest sign of intolerance the dose should be reduced. At the end of the second three month period, the conteben is suspended, and patients return to hospital for this supplementary treatment: 20 days' bed rest, during which 20 Gm. streptomycin is administered intramuscularly (1 Gm. daily); 20 I.V. injections of isoniazid, 250 mg. each to adults; 400 isoniazid pills, orally, 6 to 8 daily. Patients are then discharged, following examination of the cerebrospinal fluid, and this examination is repeated six months later. This course of treatment prevents the appearance of relapses and of resistance to medication.

Acute miliary tuberculosis. Distinction is made between fine-grained, medium-grained, and coarse-grained forms, depending on the duration of the lesions or on anatomicopathologic development. The "younger" the lesion, the more rapid the therapeutic results. Thus, fine-grained acute miliary tuberculosis, when treated, disappears within 10 to 30 days; the medium-grained, within one or two months;

* German name for tibione: 4-acetyl-amino-benzaldehyde-thiosemicarbasone.



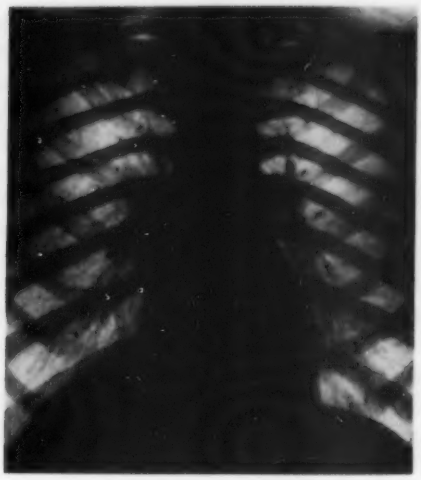


FIG. 1. (left) A roentgenogram taken of the patient, a 19 year old soccer player, on February 16, 1954. FIG. 2. (right) A subsequent roentgenogram, which was taken on March 22, 1954, shows that the cavity has completely disappeared.

the coarse-grained, within a year or more. This lesional age criterion, when applied to all clinical forms of tuberculosis, reveals the direct relation that exists between lesional age and therapeutic effectiveness. The more recent the lesion, the more effective the therapy. This fact constitutes the key to the entire concept the author developed with respect to defense against tuberculosis.

Clinically, fine-grained acute miliary tuberculosis does not demonstrate any physical pulmonary symptoms; diagnosis is based on routine roentgenogram procedure. Very abundant seeding is present, but it is so fine that it can pass unnoticed unless the roentgenogram is examined very carefully. It is always accompanied by tuberculous meningitis. Its fundamental characteristic is the rapid disappearance with treatment; within two to four weeks, no image can be found.

Medium-grained acute miliary tuberculosis is the most frequent and best known form. Only on two occasions has the author seen it develop without an accompanying tuberculous meningitis. The symptomatology tends to be tumultuous, with pronounced dyspnea, cyanosis and an abundance of sibilant rales in conjunction with crepitation in both lungs. Treatment, although slower, is quite effective. The physical symptoms disappear first, after which the previously round and neatly separated nodules become blurred and give way to the reticular image described simultaneously by Debré and the author; this is nothing more than lymphangitis caused by the passage of resorbed materials. It takes two or three weeks to disappear; the resorption process being generally complete within about two months.

In this type of acute miliary tuberculosis, fatal accidents may occur from cerebral hemorrhage due to vascular tubercles. The author has seen two instances of sudden death at a time when the pulmonary miliary tuberculosis was practically cured in

roentgenologic terms, and he has also observed a case of pulmonary perforation with spontaneous pneumothorax and empyema that resulted in the patient's death. On two occasions bacilli were found in the urine with a picture of microscopic hematuria and discrete albuminuria but with no other abnormal elements in the sediment. These disappeared with treatment.

Coarse-grained acute miliary tuberculosis differs from the foregoing types in its localization in the upper lobes, in the size and shape of the nodules, and in the attendant complications. The nodules are generally about 3 mm. in diameter and stellate in form rather than round. The condition is sometimes complicated by tuberculous meningitis, or by renal, genital or epididymal tuberculosis. It regresses slowly, normally taking six months to a year to disappear.

Adenopathy. These cases are also classified into small, medium or large, depending on their duration. "Small" adenopathy is cured in from one to two months, "medium" in two to four months, and "large" (with some exceptions) in one year or more. A study of 100 adenopathy cases, considered from the clinical and roentgenogram, showed the following results:

Size	
"Small" adenopathy	17.7%
"Medium" adenopathy	54.5%
"Large" or tumoral adenopathy	27.8%
Localization	
Hilar adenopathy	75.33%
Paratracheal adenopathy	15.44%
Hilar and paratracheal adenopathy	10.23%
Site	
Adenopathy of the right side	70%
Adenopathy of the left side	5.56%
Bilateral adenopathy	24.44%

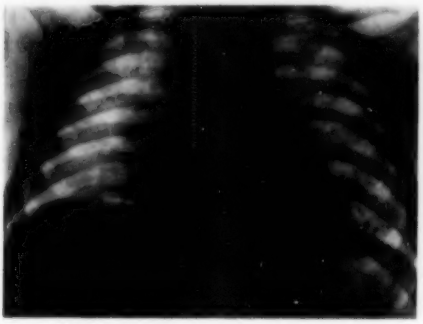
Secondary infiltrations. These vary in accordance with the adenopathy causing the infiltration, but the infiltration also acquires special characteristics of its own, depending on how it was produced. Infiltrations due to retrograde lymphogenous acute miliary tuberculosis are relatively young forms, while those due to atelectasio undergo a longer anatomicopathologic development. As a consequence, the former disappear within two to twelve weeks, compared with approximately a year for the latter. These are present in 15.5 per cent of adenopathy cases.

Early infiltrate. It is now possible to cure this condition at the time of its appearance. As is well known, this lesion was formerly the point of departure for the whole dismal chain of events which characterize chronic tuberculosis in the adult. Such patients passed from pneumothorax and pneumoperitoneum to hospitalization, pneumectomy, and a sequence of family and social changes. With present-day therapy, they can be totally cured at the onset of the illness. Early infiltrates which are discovered before any symptoms are produced disappear within two to six weeks. When diagnosis reveals the classic symptoms of hemoptysis—fever, cough, etc.—

the disease is already quite far progressed and will take three to six months to be cured; when diagnosis is late and the patient has undergone a number of cavity ruptures, the condition may disappear in a year, or it may never do so.

Clinically and roentgenologically, we very frequently find the infiltrate cavitated with sputum or with bacillary gastric content. There is a certain difference between the early cavities encountered in the course of systematic investigation and those found when the patient appears for consultation of his own accord, even when the symptoms are not alarming. In the latter case the cavities are normally clearcut, like a ticket punch, with no pericavitary reaction.

Figures 1 and 2 illustrate the case of a soccer player. The first roentgenogram was taken three days after he had played a championship game. The only physical symptom was a slight cold. With treatment, the disappearance of the cavity and the bacilli of the gastric content was rapid. Nevertheless, we cannot speak of the disappearance of the cavity until this has been demonstrated with the aid of tomography.



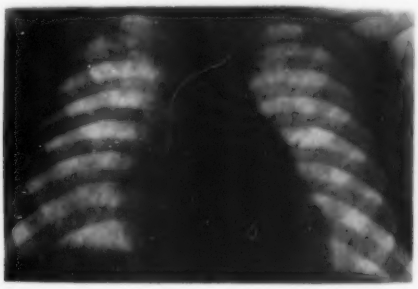


FIG. 3. (left) A roentgenogram taken on October 7, 1952, two weeks after the occurrence of hemoptysis. FIG. 4. (right) A roentgenogram taken of the same patient on July 17, 1953. The cavity and infiltration have disappeared, and a few hard, stabilized nodules remain.

When the infiltrate is seen in a patient with the classic set of symptoms, the effectiveness of the treatment is surprising, although it does not become evident until after two or three weeks. After that the regression of the clinical symptoms is very rapid, while the roentgenological regression is slower; by the end of about three months the cavity always disappears and the lesion becomes markedly reduced. It is very important that during this time the bacilli should disappear at the same rate as the expectoration. In order to determine the rate of cure in such patients it is necessary to use all available means, particularly tomography and bronchoscopy. Inactive fibrous residua often remain, and these must be watched fairly frequently. It is certain, however, that these patients will be spared surgery—pneumothorax or pneumoperitoneum—to which they were formerly invariably subjected.

Figures 3 and 4 show the development in a case identical with others of the same type. The process shown is one which could almost be called advanced in terms of the length of its anatomicopathologic course (the patient's illness dated from a

TABLE I

*Average Duration of Treatment Required in the Various Types of Acute Tuberculosis to Achieve Their Roentgenological Disappearance**

1. Tuberculous meningitis (disappearance of clinical symptoms):	
mild	5 to 12 days
medium intensity	3 to 6 weeks
grave	3 to 6 months
2. Acute miliary tuberculosis:	
fine-grained	10 to 30 days
medium-grained	1 to 2 months
coarse-grained	1 year or more
3. Adenopathy:	
small	1 to 2 months
medium	2 to 4 months
large	approx. 1 year
4. Infiltrations:	
due to lymphogenous acute miliary tuberculosis	2 to 12 weeks
due to atelectasis	approx. 1 year
5. Early infiltrate:	
without symptoms	2 to 6 weeks
with symptoms	3 to 6 months or more
late diagnosis	over 1 year, or never
6. Pleuritis:	
exudative pleuritis	1 to three months

* Treatment must continue in all types, even where symptoms are not present, in accordance with the scheme indicated.

year previously). There had been a highly dramatic onset and subsequent course that developed quite favorably as soon as the specific treatment was initiated. This demonstrates that the period in which it is possible to achieve cures without major pulmonary sequelae is of considerable duration, and that practically all incipient forms can benefit from specific treatment.

The therapeutic scheme followed in these initial forms of tuberculosis in the adult is the following: 40 to 50 Gm. streptomycin I.M. (1 Gm. daily); 30 I.V. injections of isoniazid of 250 Gm. each (5 cc.); 600 isoniazid pills, orally. At the end of this first phase, three 0.05 Gm. conteben pills are administered daily for two months. At the slightest symptom of intolerance, this dosage is reduced to two pills daily, or to one. At the end of two months, a new treatment is initiated combining streptomycin and isoniazid in the same quantities, again followed with conteben if necessary. The alternation of both types of therapy assures their effectiveness; in more than 100 cases followed with this procedure, the author has had only one failure, and

this was due to irregular treatment by the patient. General experience demonstrated that when such a vigorous treatment is applied at the onset, the majority of cases requires no surgery.

Exudative pleuritis. This is always a recent lesion and it responds promptly to treatment, taking from one to three months to disappear. Table I shows the times required for the lesions to disappear in relation to the presumed duration of the condition.

SUMMARY

The author is of the opinion that with the means now available it is easy to cure acute tuberculosis, in whatever form it presents itself.

The acute forms of the onset of chronic tuberculosis are characterized by a substantially long period in which it is still possible for therapy to be effective. With this in mind and with his extensive experience, the author states with certainty that it is possible to prevent 90 per cent of acute cases from becoming chronic. The use of both therapeutic and prophylactic resources in treating the majority of incipient patients can within a few years largely eradicate chronic tuberculosis. Society will no longer need to maintain a system of sanatoriums to care for such patients as remain, since their problem, which is nearly always a surgical one, can be handled in the general hospitals.

NOTICE

A course in "Newer Developments in Cardiovascular Diseases" will be given at The Mount Sinai Hospital, New York City, October 11–15, 1954, under the auspices of the American College of Physicians. As the title implies, the recent advances will be stressed. Doctors Arthur M. Master and Charles K. Friedberg will direct the course and prominent cardiologists and cardiac surgeons will participate.

Antibiotic Therapy of Rickettsial Diseases*

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Treatment of the rickettsial diseases of man with broad-spectrum antibiotics is a relatively recent development in therapeutics, since chloramphenicol, chlortetracycline, and oxytetracycline were first described in the interval from 1947 to 1950.[1–3] Nevertheless, the few years that have elapsed since 1947 have provided the medical practitioner with detailed, reliable information regarding the usefulness of these three antibiotics in a variety of diseases. The present report summarizes our experiences and that of many of our colleagues who have utilized these antibiotics, both in the laboratory and in the clinic, in the never-ending and age-old battle against the rickettsial diseases of man.

When initially examined in the laboratory, all three antibiotics were shown to inhibit the growth of all rickettsiae with which they were tested, although none of the antibiotics was found to be rickettsiocidal.[4–7] The first of these characteristics was manifested by prolongation of life of infected laboratory animals or embryonated eggs, or by the actual reduction of mortality in such hosts. The failure to sterilize the tissues of treated infected animals was demonstrated by the successful isolation of the infecting rickettsial agents from animals during chemotherapy or immediately following recovery from disease.

As soon as the first of the broad-spectrum antibiotics had been shown in the laboratory to have potential therapeutic value against the rickettsial agents, animal and human pharmacologic studies were initiated to investigate the acute and chronic toxicity of this drug. Subsequent studies on the other two showed that all three were well tolerated orally in normal individuals in dosages large enough to produce blood levels of antibiotic sufficient to inhibit growth of rickettsiae.

General remarks on clinical use of the broad-spectrum antibiotics. The first antibiotic to be employed clinically in therapy of rickettsial diseases of man was chloramphenicol, used in treatment of epidemic and murine typhus by Payne and colleagues in La Paz, Bolivia,[8] and Smadel and co-workers in Mexico City,[9] late in 1947 and early in 1948. Dramatic therapeutic responses were reported by both groups even though the dosages employed are today considered minimal. These early studies are probably to be remembered mainly because they stimulated further investigation, and they demonstrated that the antibiotic was safe for administration to severely ill patients.

* Reprinted from ANTIBIOTICS AND CHEMOTHERAPY, 4:792–802 (July) 1954.

Clinical experience with chloramphenicol accumulated rapidly and was quickly supplemented by similar experience with chlortetracycline* and oxytetracycline.† On the basis of this clinical material, the following dosage schedule is considered optimal for all three antibiotics: an initial loading dose of 50 to 60 mg./Kg. body weight, followed by daily maintenance doses of 50 to 60 mg./Kg. in three or four divided doses given until the patient becomes afebrile. This schedule has been used extensively in treatment of a number of rickettsial diseases and may be assumed to hold with each specific disease mentioned in this report.

Although the antibiotics under discussion are considered to be nontoxic in the dosages just outlined, certain undesirable side effects have been noted with some frequency—namely, nausea, vomiting, or diarrhea. Where these are a problem, the antibiotic may be administered more frequently in proportionally smaller doses, or temporarily discontinued.

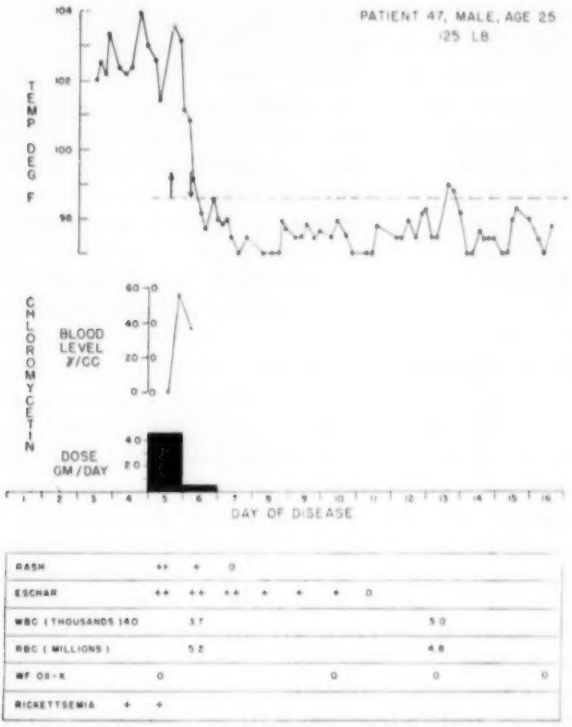

FIG. 1. Clinical chart of scrub typhus patient treated with chloramphenicol on fifth day of disease.

* The trademark name of Lederle Laboratories, Division of American Cyanamid Company, for chlortetracycline is Aureomycin.

† The trademark name of Chas. Pfizer & Co., Inc., for oxytetracycline is Terramycin.

TABLE I

Results in Scrub Typhus. Reproduced from Annals of The New York Academy of Science, 1952, Bailey and Ley[17]

Scrub Typhus Patients Treated with Chloramphenicol, Chlortetracycline, Oxytetracycline or Para-Aminobenzoic Acid

Therapy	Number of Patients	Av. Duration of Fever After Treatment (Hrs.)	Fatalities
Chloramphenicol	94	31	0
Chlortetracycline	30	25	0
Oxytetracycline	46	37	0
PABA	15	89	0
		Duration of Disease	
None	19	17 days	1

Blood dyscrasias have been reported in rare instances in which chloramphenicol therapy has been employed, especially over lengthy periods.[10–14] However, there is no conclusive evidence that aplastic anemia results more frequently from administration of chloramphenicol than it does from the use of other broad-spectrum antibiotics.[15] Regardless of which antibiotic is used, the incidence of this complication is so low that it should not influence the decision to use these agents in therapy of the rickettsioses. This group of diseases is characterized by mortality rates which overwhelmingly exceed the risk of a serious blood dyscrasia which might result from specific therapy.

Clinical use of the broad-spectrum antibiotics. Scrub typhus fever will be used as a model for discussing the clinical use of antibiotics in rickettsial diseases because of our own greater experience with this disease. The immediate effect of chloramphenicol on the clinical course of a scrub typhus patient is well illustrated in figure 1.

It may be seen that the patient's temperature dropped precipitously, reaching normal within thirty hours after the initiation of chloramphenicol therapy on the fifth day of disease; the 24 hour period of administration of antibiotic is indicated by vertical arrows and the black bar. The clinical diagnosis of scrub typhus was adequately confirmed by the laboratory isolation of *Rickettsia tsutsugamushi* from the patient's blood on the fourth and fifth days of disease. A diagnostic rise in Weil-Felix OX-K agglutination titer was not observed in this patient.

This clinical record was selected in order to provide an opportunity to discuss the relative efficacies of the laboratory procedures utilized to confirm the diagnosis of scrub typhus in the patient. Diercks has shown that isolation of the rickettsial agent is the most accurate diagnostic aid, since it was positive in 93 per cent of 127 patients with proved scrub typhus.[16] Of the serologic procedures, the OX-K agglutination reaction gave a total of 75 per cent positive reactors, and the complement fixation technic gave positive results in only 50 per cent of the proved cases.

Therapeutic results with chlortetracycline and oxytetracycline have paralleled those with chloramphenicol, and a summary of our experience with the use of these antibiotics in treatment of scrub typhus during the last five years is presented in table I.[17]

Ninety-four Malayan patients with scrub typhus have been treated with chloramphenicol which has produced defervescence in an average period of 31 hours. Similar information is presented for 30 patients treated with chlortetracycline and 46 treated with oxytetracycline. Although the speed with which the fever abated after start of antibiotic therapy varied from 25 hours with chlortetracycline to 37 hours with oxytetracycline, all three antibiotics produced highly satisfactory clinical results—the patient changed from an extremely sick, toxic individual to an alert, afebrile, active person in 24 to 36 hours. Little more can be desired in a disease that generally produced 17 days of fever and caused death in 1 person of every 15 in Malaya before the advent of the antibiotics.

It is our thesis that this dramatic clinical response of the scrub typhus patient to therapy is a result of the rickettsiostatic properties of the antibiotics which essentially call a truce between the invading agent of disease and the patient for a period of five to seven days. The eventual "cure" of the patient rests with the development of his immune defense against the disease. Assuming that the patient requires about two weeks before the antigenic stimulus of infection produces an immune state, we may expect that some patients given the short course of therapy before the seventh day of disease may experience a relapse or recurrence of infection before their immune defense is fully developed. This actually proves to be the case, as shown in figure 2 in which the incidence of relapse is plotted against the time after onset at which a 24 hour course of therapy was started.

Over three fourths of 13 patients treated within 24 hours after onset of illness experienced a recurrence of infection within seven days after the short course of

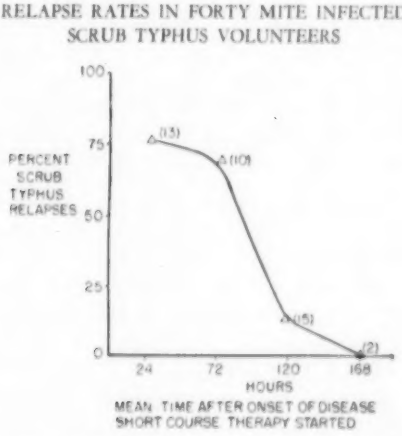

FIG. 2. Effect of time of treatment on relapse rate in scrub typhus.

antibiotic therapy was discontinued. The proportion of relapses was 7 of 10 patients when treatment was delayed until the third day of disease, and dropped to 2 of 15 patients, when delayed until the fifth day of disease. No relapses have been observed in persons treated on the seventh day of disease, or later, either in the 2 patients mentioned in figure 2 or in the 49 other patients presented in figure 3.

Further information in support of the idea of the interaction of waning chemotherapeutic control and waxing immunologic response as concerned with relapses is presented in figure 3. The normal development of OX-K antibodies in 19 patients who received no antibiotic therapy is shown at the top, where it may be seen that the geometric mean of OX-K antibody titers reached a peak titer of 1:1280 on the twentieth day of disease, and fell to a titer of 1:640 by the twenty-eighth day. It is of interest that on the twelfth day of disease, at the time the antibody titer was rising, the temperature began to fall and reached normal levels by the seventeenth day.

The course of events in 49 patients who received antibiotic therapy late in the first week of disease (seventh day on the average) is shown in the next section of the figure. In this instance the antibody titer rose to a maximum of 1:320 on the sixteenth and twentieth days of disease and fell to 1:160 by the twenty-eighth day. This group of patients responded well to treatment and experienced no relapses. It is interesting to note that at the time the patients might have been expected to relapse, a week after cessation of therapy, the mean antibody titer was between 1:160 and 1:320.

On the other hand, the next group of 34 patients treated early in the first week of disease (third day, on the average) responded well to therapy, but 62 per cent of this group experienced a relapse. It may be seen that by the seventh day after antibiotic therapy was discontinued, at the time relapses were occurring, the mean OX-K antibody titer was only 1:40, the same as it had been on the fourth day of disease. The maximum antibody titer of 1:320 was attained on the twentieth day of disease, and persisted at a titer of 1:160 on the twenty-eighth day.

It is pertinent to note that in all 3 groups thus far described peak antibody titers were observed on the twentieth day of disease, irrespective of whether or not antibiotic therapy had been given, and that although the maximum titers in the treated groups were somewhat lower than that of the group given no antibiotic, these differences are not statistically significant, i.e., they could be expected to occur more than once in 20 such groups of patients on the sole basis of chance variation.

The last group of 18 patients presented in figure 3 requires additional comment. They were immunized against the Karp strain of *R. tsutsugamushi* by the viable vaccine-chemoprophylactic method.[18] This procedure has so far been applied to human immunization only with the scrub typhus agent, but was employed earlier by Weiss and his South African co-workers for the immunization of sheep against the rickettsial disease, heart water.[19] The 18 men in the suppressed disease group received an infective dose of *R. tsutsugamushi* and subsequent oral doses of chloramphenicol carefully spaced so that clinical manifestations of disease did not appear but immunity developed. None of these individuals developed clinical signs of disease after chemoprophylaxis was stopped, yet all were resistant to subsequent re-

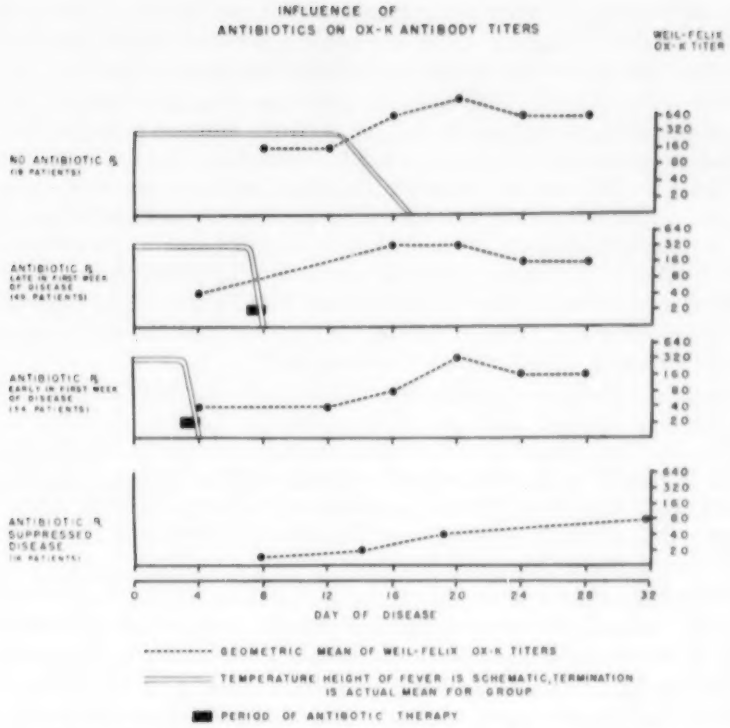

FIG. 3. Relation of time of treatment to antibody response in scrub typhus.

infection with the Karp strain of the agent. Although they were immune, this group developed a mean OX-K antibody titer of only 1:40 by the twentieth day after the time when they would have developed disease, had prophylaxis not been given. The maximum mean OX-K antibody titer of 1:80 was reached only after 32 days.

These serologic observations, like those of other investigators, indicate that the development of OX-K antibodies is correlated generally with the development of the immune state in the naturally infected patient. However, the correlation is not absolute even under these circumstances and it breaks down almost completely under the conditions of immunization by the viable vaccine-chemoprophylactic procedure.

The subject of relapses deserves some additional comment. They have been observed primarily in scrub typhus patients treated with any of the three antibiotics, although they have been reported for murine typhus patients treated with chloramphenicol.[20] All such recurrences of infection have responded well to a second course of therapy with no indication that the rickettsial agent has developed resistance toward the therapeutic agent.

The therapeutic results obtained with the three antibiotics in treatment of the rickettsial diseases of man are presented in summary form in table II.

This information has been culled from available case reports in the literature. For each disease, the response to the antibiotic is measured by the average length of the febrile period between initiation of therapy and defervescence.

A total of 26 epidemic, or louse-borne, typhus patients have been treated with chloramphenicol by Payne[8] and by Smadel[9]; 4, with chlortetracycline by Pu[21]; and 32, with oxytetracycline, by Knight and Ruiz Sánchez,[22] by Killough,[23] and by Zapff-Gross.[24] The response times for the three antibiotics are two, three, and four days, respectively. Only two antibiotics have been reported to have been used in the treatment of recurrent epidemic typhus, or Brill's disease. Chloramphenicol produced defervescence in about four days in each of 2 patients reported separately by Murray and colleagues[25] and by Knight and Ruiz Sánchez.[22] Chlortetracycline caused disappearance of fever in two days in 2 patients reported by Blumberg and co-workers[26] and in 1 patient treated by Schoenbach.[27]

In murine, or flea-borne, typhus fever, chlortetracycline has eliminated pyrexia in two days, as reported in a total of 64 patients by Knight and colleagues,[28] by Ruiz Sánchez,[20] by Giroud and his French colleagues,[29] and by Knight and Ruiz Sánchez.[22] The 17 patients treated with chloramphenicol by Ley and colleagues[30] and by Ruiz Sánchez,[20] and the 5 patients who received oxytetracycline in the hands of Bauer and co-workers[31] and Knight and Ruiz Sánchez[22] all became afebrile approximately three days after beginning therapy.

Although the subject of antibiotic therapy of scrub typhus has already been adequately covered, the essential data are included in this chart for comparison. It may be seen that all three antibiotics produce defervescence in about two days.

Thirty-one Rocky Mountain spotted fever patients have been treated with chloramphenicol by Pincoffs[32] and by Parker,[33] 13 have been treated with chlortetracycline by Ross and colleagues[34]; and 9, with oxytetracycline by Bauer[31] and by Powell.[35] The response times were four, three, and four days, respectively, for the three antibiotics.

A total of only 25 patients with the mild rickettsial disease, rickettsialpox, have received antibiotic therapy. Rose[36] reports that defervescence occurred in about two days, regardless of which antibiotic was used.

The African tick-borne fever entity includes patients with boutonneuse fever as well as those with South African tick bite fever, in accordance with the recommendations of the World Health Organization Technical Report No. 23.[37] Chloramphenicol has been employed in the treatment of 4 patients by Janbon and colleagues[38] and 1 patient by Fouquet and Morin,[39] with a response time of three days. Chlortetracycline has been used with 2 patients by LeGac and Rouby,[40] 8 patients by Henderson and co-workers,[41] and 30 patients by Gear,[42] and has produced defervescence in about three days. Fifty-nine such patients have received oxytetracycline, and in these the response times reported by Nina[43] and by Baussay[44] have been two days.

In recent years Q fever has attracted increasing attention both in Europe and in the United States, and the therapeutic reports in the literature have been increasing rapidly. Chloramphenicol has been used in a total of 24 patients and has terminated

TABLE II

Antibiotic Therapy of Rickettsioses

Disease	Treatment and Response		
	Antibiotic Used*	Number Patients	Days Febrile After Start Rx
Epidemic typhus (louse-borne)	C	26	2
	CT	4	3
	O	32	4
Brill's disease	C	2	1
	CT	3	2
Murine typhus (flea-borne)	C	17	3
	CT	64	2
	O	5	3
Scrub typhus (mite-borne)	C	94	2
	CT	30	2
	O	46	2
Rocky Mountain spotted fever	C	31	4
	CT	13	3
	O	9	4
Rickettsialpox	C	8	
	CT	9	2
	O	8	2
African tick-borne typhus	C	5	3
	CT	40	3
	O	59	2
Q fever	C	24	3
	CT	52	5
	O	7	3

* C = Chloramphenicol; CT = Chlortetracycline; O = Oxytetracycline.

fever in three days as reported by Zorafonetis and Bates,[45] by Clark and Lennette,[46] by Fellers,[47] and by Scuro.[48] Fifty-two patients have received chlortetracycline with an average response time of five days as reported by Clark and Lennette[46] and by Fellers.[47] Giunchi[49] and Anderson[50] have reported treatment of 7 patients with oxytetracycline which produced defervescence in an average period of three days.

DISCUSSION AND SUMMARY

It is apparent that all three broad-spectrum antibiotics currently available are effective in treatment of rickettsial diseases of man in daily oral doses of 50 to 60 mg./Kg. body weight, supplemented by an initial loading dose. With certain dis-

eases, particularly scrub typhus, the institution of specific therapy early in the course of disease has resulted in recrudescence of illness after the rickettsiostatic effect of the drug has been dissipated and before the patient has had sufficient time to develop his own immunologic defense. In such instances an additional short, 24-hour course of antibiotic is indicated about six days after the end of the first course to prevent relapse until the patient's immunity mechanisms can control the infection.

It is difficult to convey the significance and the extent of the changes in therapy of rickettsial diseases that have resulted from use of the broad-spectrum antibiotics. Of the 588 patients mentioned in this review, who have been treated by various groups of investigators in different parts of the world, not a single death has been reported in persons receiving adequate dosages of antibiotic before the terminal stages of disease. Furthermore, we know of no unpublished instances in which the broad-spectrum antibiotics, given a reasonable chance, may be said to have failed and to have permitted the rickettsioses to proceed to fatal conclusion. The present results seemed almost impossible only a few short years ago, and today one recalls with difficulty the prolonged febrile courses and the frequent deaths of patients with rickettsial diseases. The efficacy of these therapeutic agents and their rapidity of action have increased the need for early diagnosis of the rickettsioses and have modified the application of immunization and vector control under certain circumstances. Thus, it may be more practical to treat the few cases of rickettsial disease that develop annually in an endemic area than it is to apply control measures to the entire population exposed to risk. We have in mind, for example, Rocky Mountain spotted fever in the central Atlantic states or boutonneuse fever in some Mediterranean areas.

The clinical experience with specific rickettsiostatic antibiotics summarized here is so satisfactory that there is no longer a strong motivation to search for other rickettsiostatic agents. However, should an antibiotic be found which in the laboratory is both rickettsiocidal and nontoxic, it would be worthy of immediate clinical investigation.

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MEDICAL HUMANITIES

Osler

Part II: Johns Hopkins To Oxford*

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Part I of this account of the life of one of the most beloved and influential physicians and professors of medicine of his day relates the birth—in Bond Head, Upper Canada, in 1849—and early life of Sir William Osler. From his youthful days in Dundas, Barrie, and Weston—where he came under the influence of "Father" Johnson and Dr. Bovell—and during his education in Toronto and McGill (M. D., 1872), and on his travels abroad, Osler showed a developing love for his profession, for books, for learning, and for men. He began his "ink-pot career" in 1869 while yet an undergraduate. As a teacher and crusader for better medical schools, his success was marked from the start at McGill in 1874, continued at Pennsylvania in 1884, and reached its height at Johns Hopkins, whose staff he joined in 1889. After his fruitful years in Baltimore, he was called to Oxford as Regius Professor—the story of which follows below.

VI

Among the cities which still pay an unnecessary Delian tribute of young lives to the Minotaur of infectious diseases, Baltimore holds a high rank. The pity of it is, too, that this annual sacrifice of thousands of lives (2,281 for 1892, not including consumption), is not due to ignorance. For more than fifty years this gospel of preventive medicine has been preached—whether they would hear or whether they would forbear—in the ears of councils and corporations; *that three measures, efficiently designed and efficiently carried out, reduce to a minimum the incidence of infectious diseases: viz., pure water, good drainage, and proper isolation of the sick.* Of sanitary essentials in a modern town, Baltimore has a well-arranged water supply; still, however, with unprotected sources and constant liability to contamination. It has nothing else—no sewage system, no system of isolation of the sick, no hospital for infectious diseases, no compulsory notification of such a disease as typhoid fever, no disinfecting station, no system of street watering, no inspection of dairies, no inspection of meat. The streets are cleaned, but so carelessly that for a large part of the year the citizens breathe a mixture of horsedung and filth of all sorts. Perhaps the best gauge of the sanitary conditions of a city is to be found in the mortality returns from typhoid fever.

In this vein, the socially-minded Osler was to plead for many years against civic indifference; and the influence of Hopkins, and especially that of Osler, played a large part in transforming Baltimore from a city that disposed of its sewage in the streets and dumped all sorts of refuse from factories and tanneries into the miserable creek in midtown called Jones Falls, to a modern metropolis of paved streets and underground conduits. But to return to the medical school: Welch and Osler,

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too, worried lest the standards of admission were so high no one could meet them. As the latter remarked: "Welch, it is luck that we get in as professors; we never could enter as students." Hopkins' requirements for this first year were: a degree of bachelor of arts or of science, a two years' premedical training in biology, chemistry, and physics, and a reading knowledge of French and German. These were high for those days, and only 18 students were able to meet them. Under Welch, whom the students dubbed "Popsey" (Osler, "The Chief," and Halsted, "The Professor"), the entering class started in very simply and lived amidst such an air of good feeling, friendliness, charitableness, and helpfulness that Cushing says rivals complained that the Hopkins group was a "Society for Mutual Admiration." Yet, largely because of Osler's personal charm, factions were brought together in Baltimore among the five medical schools in the area, and hostility and jealousy among them vanished.

More important to him personally than the many meetings, addresses, papers, journeys, which, as always, made up his life, or the new edition of his text book, the revision of which made the library "a perfect wreck—floor, tables, and chairs covered with books and journals," was the birth on December 28, 1895, of his son Revere. (Another son had been born in 1893, but had lived only one week.) Having been devoted all his life to children, Osler saw, of course, in his own son a source of the greatest happiness for the rest of his life. Hardly a letter of any length that he wrote from this day on failed to mention Revere, whom he called "Ike," or "Tommy," or "Egerton, Jr." And the boy's eventual death in World War I was the blow that virtually killed his father.

In the medical school, where above all else Osler's real fame was growing, the 15 surviving members of the Hopkins' first class were now entering their third-year clinical work, and the lively Canadian professor was finally getting his own ideas into full-scale use. In the clinical laboratory which he controlled he had started his "observation clinics" where, three mornings a week, around a couch and a table, students were taught methods of examination. Here the young men learned what examination meant: "Don't touch the patient—state first what you see; cultivate your powers of observation." And through excellent organization, subdivision of labor, and cooperation, Osler made work, for the first time, the so-called unit system. At Hopkins, this was a medical unit comprised of wards of about 70 beds each (later it became 100), a large outpatient department, and a clinical laboratory, all under the care of the Professor of Medicine. Osler had three resident assistants, whom he had nominated himself, a fourth assistant in charge of the laboratory, and four annually appointed house physicians. The first assistant was appointed for several years and was in charge when the Professor was absent; he and the other assistants were paid by the Hospital and the University. Given responsibility, they were encouraged to teach and to write, and in every way their professional development was promoted, including four to six months' vacations abroad for study. The outpatient department had a separate staff, usually men who had been senior assistants and were now practicing in the city.

Finally, in the fall of 1896, the fourth-year students came into the wards for the first time as clinical clerks. It was here, visiting with them from 9 to 11, three

mornings a week, that all felt Osler was at his best. From the pen of one of his senior assistants, Dr. W. S. Thayer, we get something of what he was trying to put over:

> Observe, record, tabulate, communicate. Use your five senses. The art of the practise of medicine is to be learned only by experience; 'tis not an inheritance; it cannot be revealed. Learn to see, learn to feel, learn to smell, and know that by practice alone can you become expert. Medicine is learned by the bedside, and not in the classroom. Let not your conceptions of the manifestations of disease come from words heard in the lecture room or read from the book. See, and then reason and compare and control. But see first. No two eyes see the same thing. No two mirrors give forth the same reflection. Let the word be your slave and not your master. Live in the ward. Do not waste the hours of daylight in listening to that which you may read by night. But when you have seen, read. And when you can, read the original descriptions of the masters who, with crude methods of study, saw so clearly. Record that which you have seen; make a note at the time; do not wait. "The flighty purpose never is o'ertook, unless the deed go with it."

Meanwhile Osler's preoccupation with public health measures continued, and he employed two methods of rousing men in the medical profession to take a definite stand on such issues: one by prodding the old societies into action through his own spirit and enthusiasm, and the other by his stirring speeches, which were widely quoted. One such speech, the "Study of Fevers in the South," was read on May 6, 1896, at the American Medical Association meeting in Atlanta. The warning was stern, the appeal especially moving:

> Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever. Gad, the seer of David, estimated aright the relative intensity of these afflictions when he made three days' pestilence the equivalent of three months' flight before the enemy, and of three ([or] seven) years of famine. . . . Of no disease is the history better known; the measures for its prevention are everywhere recognized; the incidence of its recurrence is an unfailing index to the sanitary intelligence of a community. With good drainage, pure water, and pure milk, typhoid fever goes the way of typhus and cholera. The greatest sanitary triumphs of the century have been in reducing to a minimum the mortality from this disease in the great centres of population in Europe. The mortality returns of Washington and of Baltimore, and of many smaller cities, demonstrate that we are culpably negligent in allowing this most easily preventable disease to continue its ravages. . . .

It was during the summer of this year, 1897, that Gates, of John D. Rockefeller's philanthropic staff, chanced to become interested in medicine and, though a layman, read the whole of Osler's textbook. His story, as told by Cushing, says:

> I speak of this not to commemorate my industry or intelligence but to testify to Osler's charm, for it is one of the very few scientific books that are possessed of high literary quality . . . I saw clearly . . . that about all that medicine up to 1897 could do was to suggest some measure of relief, how to nurse the sick, and to alleviate in some degree the suffering. . . . When I laid down this book I had begun to realize how woefully neglected in all civilized countries and perhaps most of all in this country, had been the scientific study of medicine. . . . It became clear to me that medicine could hardly hope to become a science until it should be endowed, and qualified men could give themselves to uninterrupted study and investigation, on ample salary, entirely independent of practice. . . . Here was an opportunity for Mr. Rockefeller to become a pioneer. . . . [Thus, after some discussion] and out of wide consultation the Rockefeller Institute of Medical Research came into being. It had its origin in Dr. Osler's perfectly frank disclosure of the very narrow limitations of ascertained truth in medicine as it existed in 1897.

In 1900 came a tempting call to the Chair of Medicine at the University of Edinburgh, called the "blue-ribbon" position in British Medicine. It was but one of

many efforts to lure him away from Johns Hopkins, and at first it seemed likely that Osler would accept. His son Revere was growing up, and he wanted the boy educated in the old country; he himself planned to retire in England not too many years hence. But two things combined to change the course of events: Osler was laid low by influenza and feared he might not be able to endure the severe Edinburgh winters, and there was a veritable storm of protest when the affair was headlined in the papers. In a note in a book some years later, Osler said he withdrew his name in the depression associated with an attack of influenza, adding, "I wonder what would have become of me at Edinboro—whiskey or John Knox? I think I should have got on with the men as I have always liked the Scotch."

So he remained for a few years more at Hopkins, busy with the multifarious activities that characterized his extraordinary career: with societies concerned with disease, and others concerned with book-collecting; with addresses on public health, medical history, and medical bibliography; with the laborious task of yet another textbook revision; with trips abroad; and always with his teaching. The prime importance to him of the last can be estimated from his own statement: that his principle contribution to medicine and to medical education lay in the fact that he was the first who "admitted students to the wards."

But his time at Hopkins was drawing to a close. On August 4, 1904, the offer of the Regius Professorship of Medicine at Oxford was made and accepted. As his friend Weir Mitchell wrote to him:

And this for you—

> Oxford to him a dearer name shall be
> Than his own Mother University.

In his acceptance, Osler gave as his reasons for a change:

> While very happy here and with splendid facilities, probably unequalled in English-speaking countries, I am over-worked and find it increasingly hard to serve the public and carry on my teaching. I have been in harness actively for thirty years, and have been looking forward to the time when I could ease myself of some of the burdens I carry at present. . . . My only doubt relates to the somewhat relative duties of the Chair. I am interested in clinical teaching, am fond of it and have acquired some degree of aptitude for bedside work which gives me a certain value in the profession. I should miss sadly the daily contact with the students, unless I could arrange for clinical work in London. On the other hand, I have a mass of unfinished literary material on hand which the academic leisure of a new place would enable me to complete.

To his friends he explained:

> I am on the down grade. . . . Better to get out decently in time, & leave while there is still a little elasticity in the rubber. It will be an awful wrench to part with all you dear boys, but I shall only cut off 4 years as I had firmly decided to chuck everything at 60.

The feeling expressed in this last remark was to be responsible, before Osler left his native shores for good, for the incident by which he is to this day remembered by many who are ignorant of his true character and accomplishments. On February 22, 1905, Osler made the first of three valedictory speeches, "The Fixed Period," and instantly brought down on his unsuspecting head a storm of vituperation and protest. In the address he said that he had . . .

two fixed ideas, well known to my friends, harmless obsessions. . . . The first is the comparative uselessness of men above forty years of age. . . . The effective, moving, vitalizing work of the world is done between the ages of twenty-five and forty—these fifteen golden years of plenty, the anabolic or constructive period. . . . My second fixed idea is the uselessness of men above sixty years of age, and the incalculable benefit it would be in commercial, political, and in professional life if, as a matter of course, men stopped work at this age. . . . Whether Anthony Trollope's suggestion of a college and chloroform should be carried out or not I have become a little dubious, as my own time is getting so short.

Next day, in headlines across the nation, the speech was heralded: OSLER RECOMMENDS CHLOROFORM AT SIXTY; and in every corner of the land for weeks, editorial comment, letters, cartoons, endless comment made an abusive uproar which was to create the term "Oslerize" as one of opprobrium. Though sorely hurt, Osler refused to make a refutation, and in later years often jokingly referred to the address in letters and in informal remarks as the "tempest my innocent and jocose remarks raised."

But his second valedictory, "The Student Life," presented in Montreal as a farewell to his former pupils, became the most widely reprinted and popular of all his essays, its theme that education is a lifelong process of adding day by day to one's knowledge and wisdom; and in his final address before the Medical and Chirurgical Faculty in Baltimore, he propounded his own lifelong philosophy, under the title "Unity, Peace, and Concord."

Shortly afterward, having endured an enormous subscription dinner in the Waldorf Astoria Hotel in New York City, he sailed for England. The brief details we get from his account book:

Sailed from New York on the Cedric on the 19th [May] almost dead! Arrived in Oxford Saturday evening [27th], went directly to Mrs. Max Müller's house 7 Norham Gardens which we had taken furnished. I was blue as indigo for the first two or three days. I was thoroughly worn out and it was six weeks or more before I felt myself.

VII

Osler's position, the Regius Professorship of Medicine, was one of the five such Chairs, (Divinity, Civil Law, Medicine, Hebrew, and Greek) founded in 1546 by King Henry VIII. To add to the salary, the Mastership of the almshouse at Ewelme was added to the post in 1617, and again in 1858 another Chair was added, the Aldrichian Professorship of the Practice of Medicine. As "R.P.M.," Osler was also automatically a Curator of the Bodley Library, a position which of course pleased him very much and of which he was to make a great deal; and he was the official Examiner for all medical degrees given by Oxford. "A special meeting of the Curators of the Bodleian Library will be holden in the Delegates' room on Friday next the 2nd of June at 5 o'clock" was Osler's first notification of duties connected with his work. "Will be holden," his biographer says, delighted him always.

After he had been properly matriculated, made an Oxford M.D., and given a seat with the Dons, he soon began to see that leisure was not for him: he had too much vigour for that, even though he did begin to fit into the new surroundings

which he had inherited from his forbears. There are several minor things that ought to be recalled about that autumn of 1905. First, the international tuberculosis congress was held in Paris. While there, Osler (who suggested it) and sixteen members of the American delegation to the congress paid tribute at the tomb of the French teacher, Louis, by whose pupils the American school of clinical medicine may be said to have been created. This touched French sentiment very deeply. Then, when he returned to England, the tercentenary of the birth of Sir Thomas Browne was celebrated, he who had always been the most favored of Osler's favorite medical men: naturalist, philosopher, scholar, biologist, author, and physician. This meant for Osler two speeches, the first at Guy's Hospital on the *Religio Medici*; the second a week later at Norwich, where he was thanked for the casket and pedestal which held the skull of Browne. There was his Bodleian Curatorship; his work in the organization of the Royal Society of Medicine out of a number of small societies; his new duties as a Delegate of the Oxford University Press; and his task at Ewelme, which he took with all seriousness, whereas others merely had collected the stipend and showed up for a visit once or twice a year.

The old almshouse at Ewelme was nearly 500 years old, built by Alice of Suffolk in the XVth century. In one of its rooms, in a rusted safe, Osler and his nephew, Dr. W. W. Francis, discovered an amazing collection of documents—deeds, indentures, audit accounts, conveyances, court rolls, some of them written in Norman French of the XIVth century, and even the original charter of King Henry VI endowing the almshouse. All were collected into a large folio entitled "Ewelme Muniments" and displayed in the Ewelme almshouse. The recovery of these old manuscripts was a heady wine to Osler's bibliophilic nature, and another opportunity of the same sort excited him to even greater activity. At about this time, the Bodley Library was enabled to recover its original copy of the First Folio of Shakespeare, called the Turbutt Shakespeare. It was secured "by public subscription," a phrase camouflaging a good deal of behind-the-scenes work by Osler, who not only gave generously himself but succeeded in getting large sums from others. "You deserve a statue in the Bodleian quadrangle," the librarian told him, astonished that this physician should be so learned in bibliography and literature as well as science.

So, in addition to his regular duties at the Oxford School of Medicine, innumerable other interests and activities continued to engage him. He travelled to America and did his part to make the British Medical Association meeting in Toronto successful; he gave the annual Harveian oration in the fall of 1906 before the Royal College of Physicians, an address which was widely commented on; he did much work on his *System of Medicine*; he was elected to the Athenaeum Club for "serious amusement"; and his election to the Bibliographical Society brought freshness where it was most needed. He was appointed consulting physician to the staff of the new King Edward Sanitorium for Tuberculosis at Midhurst, Surrey; occupied himself with the first meeting of the Association of Physicians of Great Britain and Ireland (a society in whose establishment he had had a considerable part); headed the editorial board of the new *Quarterly Journal of Medicine*; and was doing his part in the reform of educational standards, which, in England, included writing a letter to *The Times* to suggest that Oxford needed both executive and legislative modification and that the relation-

ship between the colleges and the university must be changed in keeping with the times.

Public health work, as always, continued to interest him. In an address to the International Congress of School Hygiene, he pointed out how far behind the Continent Great Britain was in methods of school inspection and especially in dental hygiene. Later in the same year, 1907, he addressed the Women's National Health Association, telling his hearers tnat a generation should see a 50 per cent reduction in the mortality rate from tuberculosis. Before the year ended, he appeared before the Royal Commission on Vivisection, a subject whose importance he had stressed for many years. And his growing concern with historical medicine is shown in his famous Linacre essay, in which he celebrates the "quickening spirit" of the great medical humanist and teacher. A year of tremendous activity, even for Osler, concluded with a hard-fought battle for the Lord Rectorship of the University of Edinburgh, an honorary position which he, a stranger and nonparty candidate, came within 200 votes of winning. "I do not believe any other human being standing as an independent candidate could have shown anything like the same result," wrote Professor G. A. Gibson in a letter congratulating Osler on the "magic influence" of his name.

VIII

In these busy, happy years immediately preceding the first World War, when he had come into such fame as is usually reserved for men after their death, and was still vigorously pursuing the many activities of his brilliant career, Osler was also beginning for the first time to feel his age. He was sixty, and had been overworking all his life. Though he usually adopted a playful attitude toward his maladies—such as sending a pebble from his garden for the Professor of Chemistry to analyse, pretending it was a stone he had passed—he suffered from acute and painful illnesses. No sooner had he recovered, however, than he was again hard at work.

In these years between 1910 and 1914, Osler did some of the most effective work of his career. In the field of public health, which had for so long engrossed him, his antituberculosis crusades were particularly notable. Indeed, Cushing feels that "Osler's greatest professional service was that of a propagandist of public health measures," first against malaria and typhoid in the wards and on the public platforms, and then in the battles to bring consumption under control. He continued his lifelong efforts in behalf of medical education in such addresses as "The Hospital Unit in University Work," and in articles written for both British and American journals. His bibliomania, long well-established, was as acute as ever. As he told the Antiquarian Booksellers, "You see before you a mental, moral, almost, I may say, a physical wreck—and all of your own making. Until I became mixed up with you I was really a respectable, God-fearing, industrious, earnest, ardent, enthusiastic, energetic student. *Now* what am I? A mental wreck, devoted to nothing but your literature. . . ." His travels to the Continent and to America, with all they entailed of meetings and addresses, continued as regularly as before. And in the midst of all this came the official recognition of his achievements: he was created

a baronet, and became Sir William Osler, *Bart.* It was an honor which gave particular pride and gratification to Canadians, who counted him still as one of themselves.

Meanwhile, the war clouds were gathering. But nonmedical problems for the most part failed to engage Sir William's attention. Politics, national or international, he did not understand and, therefore, found them a nuisance, which he brushed aside with an angry wave of his hand. The 1911 elections, he said were "beastly. . . . Plague on both their houses! The country is safe—never so prosperous if they would only shoot the newspaper editors." His own preoccupations at this time were the Silliman Lectures which he had promised to give at Yale in the spring of 1912; the cataloging of his own library; and the launching of an historical section of the Royal Society of Medicine. The lectures, on the topic of "The Evolution of Modern Medicine," he described as "a sort of aeroplane flight over the history of medicine," from the time of the Egyptian doctor Imhotep, "the first figure of a physician to stand out clearly from the mist of antiquity," to the days of modern sanitation with its organized crusade of tuberculosis. Like all Osler's lectures, they were directed to the laity as well as to the profession, for he understood the human being as well as the scientific and medical side of the principal characters.

In the early part of 1914, that year of feverish jockeying for position among the European nations, Osler continued his usual round of activities: getting up a dinner for Gorgas, medical conqueror of Cuba and Panama; speaking to the Jewish Historical Society of England on the work and influence of Jews in medicine; entertaining at his home, the "Open Arms," and working along bibliographic lines; and refusing both the presidency of the Royal Society and efforts made to induce him to stand for Parliament, on the same ground—"it is not my job." Then, on June 28, a Serbian fanatic threw a bomb, and signalled the beginning of that World War which, with minor interruptions, has continued in various parts of the world ever since.

If Osler failed to realize the seriousness of the situation, his naïvete was no greater than that of many who should have known better. On July 31, he had sent Lady Osler and Revere to America, intending to sail himself in September and had actually gone on a trip to Colonsay, Lord Strathcona's island 40 miles from the coast. After some difficulty, he and his friends returned to Oxford, where they found a changed world. The University buildings were being converted into a hospital centre. Within a few weeks, the Examination Schools were a 1,000 bed hospital, completely equipped, and in the courtyard were pavilions built to contain beds. The plan was to receive the regular army's patients from the large army hospital at Netley, where it was intended to place the wounded soldiers coming from across the Channel.

Osler was placed at the head of a War Emergency Committee formed by the British Medical Association to utilize fully all the country's practitioners. He was named Honorary Colonel of the Oxfordshire Regiment, consulting physician to a hospital in Devon supported by Lady Randolph Churchill and other Americans, and held the same position at a Canadian hospital near Netley. He at once threw himself into the new phases of an old fight, as seen in a letter to *The Times* on the very great importance of a compulsory antityphoid vaccination order for soldiers. "In war," he

wrote, "the microbe kills more than the bullet. Malaria, cholera, typhus, typhoid, and dysentery have been the scourge of armies. From the first three our soldiers are not likely to suffer; but it will be very difficult to prevent outbreaks of dysentery or of typhoid fever, of which in the South African War more men died than were killed in action. Against this we now possess an effective vaccine." But the anti-vivisectionists and the antivaccinationists put up such a howl that Osler had to go from camp to camp to appeal directly to the soldiers; and he wrote broadsides for the battle as well: thousands of copies of his penny war pamphlet were printed and distributed by the Oxford Press.

If his energies had been put to full use before the war, they were certainly more widely used now. He became consultant to the Canadian Hospital in London and Physician-in-Chief to the Queen's Canadian Hospital in Beechborough Park, Shorncliffe, as well as consultant to an auxiliary hospital organized by American women at Paignton and an officers' hospital at Lancaster Gate. Also, he regularly visited several other hospitals. As Dr. Cushing says, "It is a universal comment that whenever a difficult case turned up, or whenever anyone wanted help or advice, Sir William was sure to be on hand."

His lectures nowadays were only those which had a bearing on the war effort, like "The War and Typhoid Fever," delivered on November 20, 1914, to the Society of Tropical Medicine in London. In this he reported on every case of inoculation which had produced untoward effects, and while regretting that inoculation was not compulsory, he hoped enough of the men would take advantage of it so that at least the frightfully large mortality rate that had characterized the Boer War could be avoided. The controversy continued throughout 1915, and Osler interested himself particularly with regard to the thousands of Canadian troops who were pouring into England.

In September he paid a long-promised visit to the McGill Unit in France and saw something of the war at first hand. "I do not believe this horrid business will ever be over," he wrote in a private letter, "but we are keeping up our courage." In an address to the Leeds Luncheon Club on "Nerve and Nerves," he emphasized the importance of what is now called "morale" in warfare: "*Nerve*; the man who can best stand the rack will win." At the same time, his attitude toward reprisals, which were being advocated by many because of German atrocities, illustrates how well he kept his own balance and clung to his lifelong doctrine of "aequinimitas." "The cry for reprisals," he wrote in a letter to *The Times*, "illustrates the exquisitely hellish state of mind into which war plunges sensible men. Not a pacifist but a 'last ditcher,' I yet refuse to believe that as a nation, how bitter soever the provocation, we shall stain our hands in the blood of the innocents. In this matter let us be free from blood-guiltiness, and let not the undying reproach of humanity rest on us as on the Germans."

But an event was approaching which was to strain his own morale to the utmost limit and was to be instrumental in the opinion of his friends in hastening his death. His son Revere, after a period of service as orderly, was transferred to the artillery and his unit ordered to France. Here he took part in the great battle of the Somme,

while his father, whose incessant war work had left him a prey to bronchitis and an alarming loss of weight, was consumed with anxiety for him. Osler's fears were justified. In August, 1917, the boy was killed in action by fragments of a bursting shell. Osler wrote in his account book:

> I was sitting in my library working on the new edition of my textbook, when a telegram was brought in: "Revere dangerously wounded, comfortable and conscious, condition not hopeless." I knew this was the end. We had expected it. The Fates do not allow the good fortune that has followed me to go with me to the grave—call no man happy till he dies. The War Office telephoned at 9 in the evening that he was dead. A sweeter laddie never lived, with a gentle, loving nature. He had developed a rare taste in literature and was devoted to all my old friends in the spirit—Plutarch, Montaigne, Browne, Fuller, and above all Izaak Walton, whose *Compleat Angler* he knew by heart and whose "Lives" he loved. We are heart broken, but thankful to have the precious memory of his loving life.

Many felt as did Nancy Astor, who later wrote that the news of Revere's death was the blow that "really killed him. The men [in the Hospital] saw what had happened and we all knew his heart was broken. He went through the wards in his same gay old way, but when he got to the house—for luncheon alone with me—he sobbed like a child. It was so hard for us who loved him." "We are taking the only medicine for sorrow," Osler himself answered one of his former assistants who had written him, "—time & hard work." Hard work included active interest in the unveiling of a Roger Bacon tablet, writing to the *Lancet* on "Homebred Malaria," the usual obligation to the Bibliographical Society, the Radcliffe Infirmary, the Press, the Bodleian, revising his textbook, acting as president of the Classical Association. These took up his days; but he could not control his emotions when he was alone at night. Lady Osler writes that he was "a shadow of his former self." As the ghastly year ended, he was helping everyone who came to him, few being aware as his wife was that he might break down at any minute. He found pleasure in entertaining young people, one of whom remembered: "We were at the Oslers' our first Christmas night overseas, a great crowd of us; and Sir William was very lively and entertaining."

He was turning 69 now, and there were rumors that he was in ill health. He was advised to take it easy and responded, characteristically, by immediately embarking on a four day trip through some American hospitals being organized in the south of England, speaking to the assembled medical officers on problems that might be expected to arise, telling them of demonstrations to be given for them in London, and assuring them of a hearty welcome at 13 Norham Gardens. These addresses, to Canadian and American medical officers, came to be Osler's chief task in the last months of the war. Finally, it was over, and Sir William wrote, in an optimistic mood: "All here are so enthusiastic about the U. S. & Mr. Wilson. What a wonderful change in a few months. There may be at last a great peace."

Matters which occupied him as 1919 began were the education of the public against venereal disease, a campaign opposed by the more conservative elements in government and medicine; his scheme for postgraduate medical instruction; and an Inter-allied Fellowship of Medicine. The last named got Osler to serve as president, even though his three years overdue textbook revision and his Classical Association address were still on his agenda. Attempting to pick up where he had left off, he

was literally wearing himself out—the Tuberculosis Society meeting at the end of March; a three day special session of the British Medical Association in April; and on May 16, his presidential address before the Classical Association, entitled, "The Old Humanities and the New Science," a stirring plea for the mingling of science and the classics in the education of students. Through a study of the history of science, which falls between the realms of both science and the humanities, he had found, he felt, an agreeable middle ground for the seemingly opposed forces of learning.

On the occasion of his seventieth birthday, July 12, 1919, he was "victimized by his friends," with a celebration in his honor being held just after a meeting of the Royal Society of Medicine in London. His home was literally swamped with letters, cables, telegrams; and the medical journals in Great Britain, in the United States, and elsewhere issued special "Osler numbers" in an astounding outburst of tribute and affection. He was especially pleased by the Osler number of the Johns Hopkins Hospital Bulletin, which he remarked "left nothing to be said. The end of the number brought the thrill of the day, when I saw revealed the utter shamelessness of my life—and the true reason of our Secretary's attachment to me! A bibliography of my writings extending to 730 articles!"

But overwork and grief had left him an easy victim to an old enemy—bronchial pneumonia. He was himself aware that the fevers and coughs that were attacking him were serious and that he was drawing near the end. He called off his many engagements, withdrew from a number of his official positions, and between paroxysms one day announced in a frolicsome mood that "pneumonia at seventy is fatal; here is a list of people to give my love and good-bye to." In a detached way he also jotted down clinical notes of the progress of his sickness and sent them with messages of greeting to his professional friends, much as if he himself were attending a patient in whom they were interested. He recovered briefly, but succumbed again, exhausted by fever and bouts of coughing in the early hours of morning. In the first days of December, Dr. Archibald Malloch joined the household, and Osler said to him when the former tried to explain his illness: "Archie, you lunatic! I've been watching this case for two months and I'm sorry I shall not see the postmortem. At any rate the books are there; do you know about Michelangelo and his tomb? So pathetic! Well, it's Michelangelo and his tomb, and Osler and his Library!"

In addition to notes about his own condition, he also wrote many instructions for the disposition of his books after his death. No details were overlooked: the textbook, his manuscripts, the uncompleted *Bibliotheca Osleriana*, the promise of his brain to the Wistar Institute, and his own postmortem, cremation, and disposal of the ashes. Two operations were performed after the identification of the influenza bacillus and the development of a pulmonary abscess. At 4:30 p.m. on December 29, 1919, after a hemorrhage from his wound, Sir William Osler died quietly and without pain.

Of all the eulogies, the one that best sums up Osler and what he meant to the world and to medicine is from the pen of Professor J. G. Adami:

"So passed into history, untimely, even though he had attained unto the allotted span, the greatest

physician in history." I confess that this characterization arrested me when I read it. We are not accustomed to measure up our friends against the giants that have been. And above all it is as a friend that during his lifetime we regarded Osler; as one who possessed the genius of friendship to a greater degree than any one of our generation. It was his wonderful interest in all of us that was the outstanding feature. Above all others the Angel might write him as one who loved his fellow men, placing him foremost among those whom God had blessed. It was from his humanity, his extraordinary interest in his fellows, that all his other powers seemed to flow. On thinking over these other powers, while we admit freely that there have been greater medical men—Harvey, for example, Vesalius, John Hunter, Claude Bernard, Lister, yet when we pass in review the great physicians, those who by their lives, their practice, their teaching, and their writings, have exercised the greatest influence over the greatest number of their fellows, putting together all those powers which make the complete physician, Osler must be awarded first place. . . . Think of those years at Johns Hopkins, when Osler revolutionized the teaching of medicine and of clinical medicine in a community of seventy millions. Think of the influence wielded by his textbook, not merely among English-speaking people, but the world over, even to China and Japan. There is no physician who during his lifetime has had so profound an influence upon so great a number; no one individual who has done so much to advance the practice of scientific medicine, no one whose personal intimacy with his fellows in the profession has covered so wide an area . . .—no one, in short, who has combined in the same degree the study, practice, and teaching—the science and the art of medicine.

ACKNOWLEDGMENT

I am indebted to the Oxford University Press for permission to quote from Harvey Cushing's *Life of Sir William Osler* and to my wife for editing this manuscript and preparing it for publication.

GENERAL PRACTICE CLINICS

This new monthly section of General Practice Clinics features reports of papers delivered at current medical meetings in the United States and abroad.

The Management of Leukemia in Adults

Presented by DAVID A. KARNOFSKY, M.D. (Memorial Center for Cancer and Allied Diseases) before the New York State Medical Society Annual Meeting, New York City, May 14, 1954.

Chronic myelogenous leukemia occurs principally in the middle years, 20 to 40, and is progressive and ultimately fatal. The average survival period is three to four years, but about 20 per cent of the patients survive for five years and longer. Adequate therapy in a responsive patient will produce a decrease in an elevated leucocyte count, a spontaneous rise in the hemoglobin level, a decrease in the size of the enlarged liver and spleen, and symptomatic improvement.

The most important single method of treatment is the use of x-rays. The spleen is usually treated first with small total doses of 200 to 400 r, and this may result in prolonged remissions. As the disease progresses larger doses may be given to the spleen, and in some cases the liver and long bones are irradiated.

Radioactive phosphorus (P^{32}) is a form of total body irradiation. The usual dose is 3 to 10 millicuries, and further treatment is given as necessary. Nitrogen mustard analogues (polyfunctional alkylating agents) of particular value include HN_2, TEM, and myleran. HN_2 is given intravenously, and the usual total course of treatment consists of 0.4 mg./Kg. in two to four injections. Triethylene melamine (TEM) is given orally. The usual dose is 5 to 10 mg. the first week, and further treatment is given on the basis of the patient's hematologic response. Myleran is probably the most convenient form of treatment. The usual daily dose is 4 to 6 mg., and usually a therapeutic response occurs after 150 to 250 mg. At excessive doses all these agents produce bone marrow depression with thrombocytopenia and bleeding.

Other agents in use are: (1) urethane, which is given orally in doses of 2 to 4 Gm. per day, and after a total of 30 to 300 Gm., a hematologic response occurs. This agent produces nausea, vomiting, drowsiness, and bone marrow depression. (2) Fowler's solution is begun at 3 drops three times daily, and the dose is increased until improvement or evidences of toxicity appear. (3) 6-mercaptopurine (purinethol) will regularly produce remissions, but relapses are prompt when the drug is stopped. The dosage is 2.5 mg./Kg. per day. It is sometimes effective in

patients who have become refractory to other forms of treatment. Cortisone is rarely useful, but in far-advanced cases it may diminish hemorrhagic tendencies.

Supportive measures are important. If the patient is responding satisfactorily to an agent, it should be continued; when the disease becomes more refractory, it may be desirable to shift to the trial of other agents. Treatment should be active, because of the response that may still occur in the apparently far-advanced stages of the disease.

Chronic lymphatic leukemia has a more variable course, and it may be a fairly benign condition in some patients. It should be managed conservatively. Enlarged liver, spleen or lymph nodes may be effectively controlled with small doses of x-rays. Radioactive phosphorus may produce prolonged remissions in responsive cases. TEM may be similarly effective. Some patients may be markedly sensitive, and the initial dose is usually 2.5 mg. Further treatment is determined on the basis of the response. If adequate treatment fails to produce improvement, and if there is further depression in the platelet count and hemoglobin level, the agent should be stopped. Cortisone is sometimes very effective in these cases in causing a decrease in the size of enlarged organs and a rise in the platelet count and hemoglobin level. The usual starting dose is 100 to 300 mg. per day, and if a response occurs, the dose is decreased to a maintenance level. Cortisone is also useful in the acquired hemolytic anemia which may complicate chronic lymphatic leukemia. Antimetabolites, such as amethopterin and 6-MP have not been therapeutically effective.

Acute leukemia runs a rapid course, and death usually occurs within six months in untreated cases. Adults do not respond as well as children to chemotherapeutic agents. Cortisone, and in acute situations, intravenous ACTH, have produced remissions in 20 to 25 per cent of young adults. The response is brief and second remissions are uncommon. Cortisone has not been very helpful in older adults, although it may diminish bleeding tendencies. Usually, the initial dosage is in the range of 300 mg. per day.

6-MP has caused hematologic and clinical remissions in about 15 per cent of the adult group and partial improvement in another 20 per cent. The initial dose is 2.5 mg./Kg., and although some patients may be unusually sensitive, in most instances it can be continued at this dose level. The responsive patients may be markedly improved, and on continuous therapy the remissions may last for several months or longer. The leucocyte count is not always the most satisfactory guide in 6-MP therapy, and even in the presence of leucopenia, if the bone marrow remains hyperplastic, the drug is continued. 6-MP may also be beneficial in monocytic leukemia. The folic acid antagonists have been effective in only rare cases in adults.

Thus, in leukemia in adults, while treatment is not curative, it will cause marked symptomatic relief in many patients, restore them to normal health for long periods, and may sometimes prolong life. The disease runs a variable and often prolonged course, and patients should not be discouraged concerning their immediate prognosis.

The Roentgen Effects of Isoniazid

Presented by DAVID SALKIN, M.D. (Veterans Administration Hospital, San Fernando, California) before the American Academy of Tuberculosis Physicians, San Francisco, June 19, 1954.

One hundred and six patients were involved in this study with an average age of 49 years; they had had tuberculosis for nine and one-half years, and their's were bilateral, advanced cases. Eighteen patients were fully resistant to streptomycin. These patients received at least 300 mg. t.i.d. of isoniazid without any other chemotherapy. The x-ray lesions were divided into exudative, exudative-productive, productive, productive-fibroid, fibroid, and calcified. There were 174 definite areas demonstrable. Isoniazid did not affect true fibrosis or calcification. The results on the x-ray lesions were as follows:

	Areas	*No. improved*	*% improved*
Exudative	36	23	64
Exudative-productive	16	6	37
Productive	28	4	14
Productive-fibrotic	55	2	4

In areas of infiltration, minimal lesions showed much better results than moderate or advanced lesions. The initial x-ray change was in one to three months, they reached a peak in about five months and then changed more slowly. There were better results in those patients not resistant to streptomycin. In areas of cavitation, out of 107 cavities, 5 per cent closed, 20 per cent became smaller, and 23 per cent improved. The original size of the cavity was not an important factor.

In measuring symptomatic improvement, 64 per cent had less sputum, 60 per cent had less cough and 57 per cent had a weight increase. In those showing x-ray improvement, 95 per cent showed symptomatic benefit. It was concluded that isoniazid does not cure tuberculosis from the x-ray point of view. Changes when they occur do so early and the healing of infiltrative lesions continues even though resistance to the drug has developed. Cavities stop improving when resistance develops. The exact relationship between isoniazid and other drugs remains to be determined.

Chemotherapy in Certain Forms of Juvenile Tuberculosis

Presented by DAVID M. BOSWORTH, M.D. (St. Luke's and Sea View Hospitals, New York) before the New York State Medical Society Annual Meeting, New York, May 14, 1954.

The author dealt with an analysis of the results obtained with the use of iproniazid (marsalid), and a comparison of this drug with isoniazid, largely in the treatment of tuberculosis of the bones and joints. Iproniazid was more toxic, but this was

counterbalanced by its being 27 times more effective than isoniazid in bone and joint tuberculosis. The dosage, at a maximum was 4 mg. per Kg. of body weight. Toxic symptoms include a hypertonic state with hyperreflexia and clonus, and mild personality changes. Liver damage and severe psychoses which occur in adults are not seen in children. If the dose is decreased to 2 mg. per Kg., the action of iproniazid is decreased. Central nervous system toxicity is explained by the fact that spinal fluid levels of the drug are 50 per cent higher than blood levels. Occasionally, one may force the dose to 6 mg. per Kg. for a day or two with no harm, provided the dose is immediately decreased.

Under therapy, the author's patients uniformly showed a decrease in temperature, pain relief, weight gain, euphoria, wound healing (draining sinuses and soft tissue lesions), and tubercle bacilli control. Iproniazid acted faster and was more certain than isoniazid. Reporting on 27 children of whom 26 were followed under iproniazid therapy, there were 33 proved lesions, of which 6 were of soft tissue and 27 of joint or bony structures. Of the 27, the spine was involved in 13. Ages of the children varied from 6 months to 16 years. There were no deaths among these 26 patients, although some were very sick and debilitated when first seen. Fifteen cases involved closed lesions, of which 12 were arthrodesed; 3 of these patients have been discharged.

Eleven cases included open lesions involving 14 sinuses and 8 patients had lesions draining from a bone or joint focus. All of these open lesions were completely healed by the use of iproniazid. Two of three patients with spine cases in this group also had arthrodesis. Mobile joints were obtained in six, ankylosis occurred in three. Of nine sinuses, not one healed with isoniazid but seven did with iproniazid.

One case of tuberculous meningitis which failed to respond to combined therapy with streptomycin, PAS, and isoniazid was arrested by iproniazid. Other cases involved one of rib and spine tuberculosis which also failed to respond to the above combined therapy but did respond to iproniazid. One case of hip tuberculosis, involving a draining lesion present for 16 years, healed in six weeks. There are few contraindications to iproniazid if the toxic dose is observed. The author thought it might be withheld from severely debilitated or convulsive infants whose central nervous system might not be able to withstand the toxic effects of the drug.

The Rubella Problem

Presented by SAUL KRUGMAN, M.D. (Bellevue Hospital) before the Section on Pediatrics, New York Academy of Medicine Meeting, April 8, 1954.

Rubella, a benign disease of childhood, may have serious consequences if acquired during the child-bearing period. Maternal rubella infection may be followed by fetal malformations and stillbirths. This situation has created a rubella

problem in pregnant women who have either been exposed to or have developed the disease. The solution of this problem requires (1) a knowledge of the clinical aspects of rubella, (2) a knowledge of the effect of gamma globulin in prophylaxis, (3) a knowledge of the risk of fetal malformation, and (4) a knowledge of certain personal and family considerations.

Rubella is a disease of the spring months, usually beginning in March with a peak in April or May. It can occur without a rash. Experimentally, viremia has been demonstrated in the absence of rash. There is usually either a normal or slight increase in temperature; rarely it may be as high as 103 to 104 F. The fever usually subsides to normal in 24 hours. The rash is a maculopapular eruption appearing first on the face, neck, trunk, and finally on the extremities, and it lasts one to three days. Five days before the appearance of the rash, lymph node enlargement is seen most commonly in postauricular, postcervical, and postoccipital regions. Inguinal and axillary nodes are also occasionally involved. In the majority of cases, one attack confers lifelong immunity.

Neither ordinary nor convalescent gamma globulin has been consistently effective as a prophylactic agent against rubella. There is suggestive evidence that gamma globulin may modify the disease so that no rash appears, but the fetus may be affected. Consequently, gamma globulin should only be given in those situations where a therapeutic abortion would not be considered under any circumstances after the disease has been acquired.

The current estimate of the risk of fetal malformation and stillbirth is approximately 15 to 20 per cent. This figure is about three times as great as one would expect under normal circumstances.

The factors affecting the management of the rubella problem are: (1) accuracy of diagnosis and type exposure; (2) effect of gamma globulin; (3) risk of congenital malformations; (4) personal and family considerations. All of these factors must be carefully evaluated and the solution of the rubella problem must be *individualized* in each case.

Spread of Infectious Agents in the Human Body

Presented by PAUL BEESON, M.D. (Yale University Medical School)
before the New England Pediatric Society, Boston, March 10, 1954.

Once bacteria or other agents gain access to the tissues, they spread by various means. Certain local factors play a part: (1) hyaluronidase—many organisms produce this enzyme which liquefies certain elements of connective tissue and permits the bacteria to move about freely; (2) local invitative action of the inflammation is probably of greater importance as it permits the egress of bacteria and their products; (3) differences in tissue pressure between the inflamed area and normal areas. Tissue pressure is high at the site of inflammation, exceeding

the venous pressure. This encourages the outward flow of the contents of the inflamed site. Spread may then occur through natural passages such as serous surfaces. The role of local pressure in the spread of infection is demonstrated by the beneficial effect of drainage of an abscess. Pus often spurts, because it is under such intense pressure, and drainage alone often suffices to relieve symptoms and cure disease.

Metastatic lesions of bacterial infection practically always spread by way of the lymphatics. It has been shown that ligation of lymphatic ducts prevents entrance of organisms into circulation from an inflamed area. Lymph nodes were thought to be the main filters of the body but this is not true of the normal lymph node. Only when that node becomes swollen does it exhibit significant filtering due to occlusion of sinusoid by leukocytes. Lesions of the pleura could metastasize to the brain without affecting the lung by way of the vertebral system of veins with which the pleura connects. Since these veins are valveless, the varying pressure caused by coughing or straining could reverse the blood flow and contribute to intracranial infection.

Bacteria do not grow in the bloodstream, and the continued presence of bacteria in the blood indicates a continuous seeding of the blood from some focus. Patients with bacterial endocarditis were studied by catheterizing various vascular channels, e.g., artery and vein of various viscera, the right auricle, vena cava, and hepatic vein. It was found that blood having traversed some tissues had its bacterial count reduced. This reduction occurred most significantly in the liver, which eliminated practically all the organisms—this function being maintained even in the moribund animal.

Antibiotics in the Prevention and Treatment of Infection in Newborn and Premature Infants

Presented by RALPH V. PLATOU, M.D. (Tulane University Medical School) before the University of Colorado Medical Center, Denver, March 24–26, 1954.

In the routine use of antibiotics, the author thought the desiderata should include agents with a wide bacterial spectrum and an easily attained therapeutic level; agents that were convenient, practicable, inexpensive, and with minimal side effects. The agent which most closely approaches these desiderata is terramycin, according to the author.

The indications, other than obvious infection, for routine prophylaxis were: premature rupture of the membranes, precipitate "dirty" delivery, a septic mother, "outside" delivery with details unknown, difficult resuscitation with prolonged intratracheal manipulation.

The agents available for routine prophylaxis were listed as penicillin, streptomycin, sulfonamides (sulfadiazine), any combination of these, and terramycin.

The author preferred terramycin, which was given as follows: terramycin hydrochloride 1.0 mg./cc. in one-half strength normal saline, 5 mg./Kg. per 24 hours, subcutaneously. With sustained therapeutic levels, there were minimal or no side effects. The regimen outlined is for prophylaxis only. Dosage levels for therapeutic use are somewhat higher.

Fetal and Neonatal Blood Formation

Presented by IRVING SCHULMAN, M.D. (New York Hospital) before the Section on Pediatrics, New York Academy of Medicine Meeting, New York, N. Y., April 8, 1954.

The average blood values of full term infants, taken from cord blood, are hematocrit 53 per cent, hemoglobin 16.2 Gm. per cent, and RBC 4.8 million. The most rapid rise occurs in the second trimester of pregnancy and levels off in the third trimester. With the great growth that occurs in the third trimester, the baby must produce large amounts of blood to maintain its status. They have determined that the blood volume of a 1,000 to 2,000 gram baby on the first day is 108 cc./Kg., the values being affected by the amount of blood passed to the baby before the cord is cut. There is an average of 105 cc. of blood in the placenta; if the cord is not clamped immediately, 51 per cent is delivered in one minute, 79 per cent in five minutes, and 91 per cent in 10 minutes. In the baby whose cord clamping is delayed, the hemoglobin and RBC are higher than if it were done sooner.

In the premature baby there is a steady fall in both adult and fetal Hgb. for the first six weeks of postnatal life. Then there is a sudden rise in adult Hgb., with some slight increase in fetal Hgb., which then falls off again. For the first 16 weeks of postnatal life there is more iron available than is utilized. At 16 weeks, all available stores of iron are apparently used up, and unless iron is administered Hgb. production will decrease. If iron is given at the fifteenth week, there will be a smooth rise in the production of adult Hgb.

The anemia of early infancy results from almost complete cessation of blood formation very soon after birth with recommencement in about five to eight weeks. Iron is not needed until the infant is about 16 weeks old. The premature baby has a slight element of a hemolytic component, but this contributes only slightly to the anemia of prematurity. The changes in a full term infant are almost identical with that of the premature infant. It is believed that the O_2 concentration of the blood is inversely related to the total amount of hemoglobin.

On the basis of these studies, the author gave fewer transfusions to the children on his wards than had been done previously. Infection, malnutrition, and general debility were considered to be indications for transfusion, since in such cases the infant might not be able to express its own hematologic activity.

Mucoviscidosis: Evaluation of Antibiotic Therapy

Presented by HARRY SHWACHMAN, M.D., P. CATZEL, M.B.B.CH., D.C.H., P. R. PATTERSON, M.D. AND M. STOPPELMAN, M.D. (Children's Hospital, Boston, Massachusetts) before the American Pediatrics Society, Buck Hill Falls, Pa., May 3–5, 1954.

The authors present observations made on over 120 patients with mucoviscidosis treated with continuous broad-spectrum antibiotics. They feel that the prognosis in general is dependent on the severity and rate of progression of pulmonary involvement; emphasis was therefore placed on the pulmonary aspects of the disease. The patients presented had had at least a full year of continuous therapy with aureomycin or terramycin. Doses used and recommended by the authors were 5 to 10 mg./Kg. of aureomycin or terramycin, modified as follows: infants were given at least 50 mg. per day and older children were given a maximum dose of 250 mg. four times daily.

A comparison of the chest roentgenogram at the onset of therapy with the follow-up film in 99 patients analyzed showed progression of the process in 57 per cent, static condition in 24 per cent, improvement in 5 per cent and relatively normal films in 15 per cent.

In an analysis of the age of death of 42 patients who succumbed during the five year period of 1945–54, the average age of death was found to be 45.2 months. This figure was in sharp contrast to the average age of death before the introduction of broad-spectrum antibiotics, which was 12.8 months. The authors conclude that prolonged and continuous broad-spectrum antibiotic therapy is effective in improving or slowing the progression of pulmonary pathology in mucoviscidosis.

Recent Developments in Specific Diagnosis of Poliomyelitis

Presented by JEROME T. SYVERTON, M.D. (University of Minnesota School of Medicine) before the Symposium on Poliomyelitis, Cincinnati Academy of Medicine, April 20, 1954.

A stable strain of human epithelial cancer cell (strain Hela, Gey) was studied in the laboratory for over a year. The author established that these cells support the growth of poliomyelitis virus. They can be dispensed by a single apparatus in aliquots to provide large numbers of replicate cultures or to provide single cells for intimate host-virus studies. They reproduce 5 to 10 times in 5 to 10 days and they are stable in serial passage.

Can these cells be used as a practical means for a rapid laboratory diagnosis of acute polio? Some 300 patients with clinical diagnosis of poliomyelitis were studied. The same number of strains of polio virus were isolated from various specimens including feces, throat washings, and brain or cord tissue. Simultaneously, a specific diagnosis as to type was made. Distribution of strains (immunologic type): Type 1, 74.5 per cent; Type 2, 5 per cent; Type 3, 20.5 per cent.

The results of these studies indicate that cellular cultures could be utilized in the diagnostic laboratory for the identification of a strain of polio virus, the determination of antibody levels in population groups, and the determination of antibody response to vaccines.

Prophylaxis and Treatment of Measles and Diphtheria

Presented by SAMUEL KARELITZ, M.D. (The Willard Parker) before the New York State Medical Society Annual Meeting, New York, May 14, 1954.

Antibiotic therapy of the bacterial complications of measles was discussed. Fifty mg. per Kg. of body weight of aureomycin for four days, or 300,000 units aqueous penicillin on admission, avoided pneumonia or cured it when it was once established. In untreated cases, there was an incidence of 23.2 per cent complications. Bicillin prevented complications in 59 out of 61 children; the remaining two having staphylococcal pneumonia and a bacteremia. With larger doses of aqueous penicillin (600,000 units on alternate days for three doses) in 67 patients, all complications were cured or none developed. In untreated controls temperature was still elevated above 100 F. on the sixth day after the onset of the rash, whereas in treated cases it was less than 100 F. on the fourth day. The difference in duration of fever may be due to the elimination of manifest bacterial infection by antibiotics.

Gamma globulin given after the appearance of Koplik spots to be effective for modification required doses of 10 to 50 cc., if the rash had not appeared. Gamma globulin given prophylactically in the first six days after exposure prevented or modified the disease with almost quantitative regularity, but it is a passive agent and protected for only two to four weeks. To date, the author knows of no specific therapy for measles.

As infants respond to diphtheria toxoid, the author recommended immunization after the first month, using the polyantigen mixture with injections at the third, fourth, and fifth months, a booster dose at one year and again in alternate years until the child enters school. Booster doses of 0.2 cc. are as effective as the 0.5 cc. dose and fewer reactions are seen.

C. diphtheria can be eradicated in 75 per cent of faucial diphtheria cases by 600,000 to 1,200,000 units of aqueous penicillin intramuscularly once a day until three negative nose and throat cultures are obtained, with additional negatives before discharge. Some strains of *C. diphtheriae* are resistant and other antibiotics may be used; aureomycin or terramycin in doses of 25 to 50 mg./Kg. per day are effective. In addition, erythromycin, chloromycetin, and streptomycin have been of use. In the carrier state, penicillin or other antibiotics are usually effective. The use of antibiotics reduces the length of the hospital stay, with beneficial effects on secondary bacterial infections such as sinusitis, otitis and especially pneumonia.

Treatment of the exposed individual varies with his immune state and his

symptoms. If the patient is exposed and is immune, a booster dose of diphtheria toxoid (0.2 cc.) will suffice. If a positive throat culture is obtained, penicillin therapy should be added. Antitoxin may be deferred until clinical evidence of infection appears. When the immune status is not known, then toxoid and penicillin therapy should be given and a nose and throat culture taken; a sore throat requires antitoxin immediately.

Allergic Dermatitis

Presented by GEORGE H. CURTIS, M.D. (The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute) before the American Academy of General Practice, Cleveland, Ohio, March 23, 1954.

The most difficult and most common of the allergic dermatoses are atopic dermatitis, contact dermatitis, and drug dermatoses. Atopic dermatitis is familial, but the nature of the hypersensitivity in the offspring is not necessarily the same as that in the parents. Individuals with atopic dermatitis may frequently respond to a variety of skin tests with urticarial reactions; for this reason such tests are of relatively little value in atopic dermatitis.

The disease appears in three phases: the infantile form during the second to eighth month, which tends to disappear by the age of 2; the childhood form at the ages of 6 to 10, and the adult form, usually present between the ages of 13 to 20. In all adults with atopic dermatitis, the family history reveals atopy in 60 per cent of the cases, and there is a past history of earlier manifestations of the dermatitis in 70 per cent.

In the early phases of the infantile form of atopic dermatitis, there is vesiculation, especially of the face, and later the dermatitis becomes dry and lichenified on the flexor aspects of the wrists and neck, over the face and trunk, the dorsa of the hands, and the popliteal fossae. Most infantile eczema occurs in bottle-fed babies. In adults, foods are of less importance as allergens. Contact dermatitis may be characterized by early acute eczematous dermatitis, and later chronic dermatitis. Here there is no family history, the disease may occur at any age; it is rare in infants and common in adults, without being related to a previous history of infantile eczema. In contrast to the bilateral distribution of lesions in atopic dermatitis, contact dermatitis tends to occur at the site of contact with the offending irritant. Patch tests, which are negative in atopic dermatitis, are usually positive with the proper irritant. Skin tests, on the other hand, are infrequently positive in contact dermatitis, but usually positive in atopic dermatitis.

Drug dermatitis may occur in nursing infants if the mother is taking drugs; bromides, phenolphthalein, sulfonamides are frequent offenders. The disease is of sudden onset, is generalized, and tends to be bilateral. Patch tests and skin tests with the correct drug are infrequently positive, except in the case of biologic serums and drugs. There is no family history of drug dermatitis as a rule, and the disease is not related to infantile eczema.

In the treatment of atopic dermatitis in infants, silk, wool, feathers, milk, eggs, and wheat should be avoided. House dust should be kept at a minimum, since it contains much wool. Milk substitutes may be used until sensitivity to milk is definitely ruled out. Eggs and wheat are readded to the diet after experimental elimination and readdition show no sensitivity in the infant. Topical applications of crude coal tar, vioform in lotions and ointments are useful. Hydrocortisone topically is very useful and frequently gives dramatic relief. Intercurrent infections must be watched for during internal use of the steroids. Group psychotherapy has also been found useful in the adult form of the disease. Contact dermatitis and drug eruptions may be treated by topical soothing lotions, antipruritic ointments; by cortisone, hydrocortisone, or adrenocorticotropin given orally or parenterally in severe cases. The use of steroid hormones should be continued for two to three weeks, inasmuch as the natural course of the disease may require that time for resolution. An earlier withdrawal of the hormone may lead to a recrudescence of symptoms.

Prescribing Adequate Nutrition

Presented by ELMER L. SEVERINGHAUS, M.D. (Hoffmann-La Roche, Inc., Nutley, New Jersey) before the Ohio State Medical Association Annual Meeting, Columbus, April 14, 1954.

Considerations in determining adequacy of nutrition were discussed by the author. Evidences of protein deficiency include edema, anemia, decreased immunity, delayed healing of scars, senile osteoporosis. Fat is a condensed source of energy and provides needed unsaturated fatty acids. Signs of deficiency are emaciation, weight loss, dry skin, and dermatitis. Carbohydrate serves as a source of calories and is largely interchangeable with fat. Since it is metabolized more quickly than fat, it must be ingested more frequently; most people require some carbohydrates every 24 to 48 hours. Evidences of deficiency are hunger and ketosis.

The minerals necessary for life include calcium, magnesium, phosphorus, sodium, potassium, iron, and iodine. Vitamins are best defined as functional catalytic materials rather than in terms of the diseases produced by individual deficiencies. The following facts are known: (1) Vitamin A affects growth. (2) Vitamin D is a catalyst for transformation of organic P to PO_4. (3) Vitamin K is concerned in the manufacture of prothrombin in the liver. (4) Vitamin E is an antioxidant, fat soluble. (5) Vitamin C is also a water-soluble antioxidant; it maintains the integrity of endothelium and is necessary for hemoglobin formation. (6) Vitamin B complex act as coenzymes aiding metabolic action; they are usually combined with phosphoric acid and with other groups. Deficiency of one B vitamin can masquerade as a deficiency of another in certain cases.

In clinical therapy, multivitamin preparations with adequate dosage of all im-

portant vitamins should be given for a maintenance dose. In deficiency states at least 3 to 5 times the maintenance dose is needed.

For parenteral therapy the basic components are fluid, salt, and sugar. Amino acids are necessary only when the therapy is prolonged, and vitamins are only rarely needed. The obese patient requires restricted amounts of carbohydrates and fats but adequate proteins, vitamins, and minerals. The pregnant woman needs more proteins and vitamins, although the optimal amount needed to increase fetal salvage and decrease malformations is unknown. Vitamins and a generous supply of milk are extremely important to the health of children.

Radiologic Signs of Trauma to the Growing Skeleton

Presented by JOHN CAFFEY, M.D. (Columbia University) before the Boston Hospital House Officers' Association, March 2, 1954.

While much publicity is accorded to neoplastic disease, poliomyelitis and muscular dystrophy, it is less often recognized that trauma is one of the leading causes of death in children of all age groups. Cortical thickening is one of the common results of trauma in growing children. The growing periosteum is highly vascular and is loosely attached, except at the ends of the growing bone. When traumatic injury occurs, blood and edema fluid collect between the cortex and periosteum, lifting the latter. The lifted periosteum lays down new bone, which eventually obliterates the blood-containing cavity underneath in order to join bone growing from the old cortex. This results in a cortical thickening which often involves the entire length of the shaft because of the ease with which bleeding and edema strip up the loosely attached periosteum.

Clinically, the child may present fever, leukocytosis, and tenderness over the site of trauma, causing an erroneous diagnosis of osteomyelitis or tumor to be made. In such cases, it should be remembered that bleeding can cause both leukocytosis and fever. X-rays, if taken early, will show a characteristic fraying at the end of the involved bone where the periosteum is tightly attached to cartilage. These changes present an almost pathognomic appearance; subsequent films will show the typical thickening of cortex. Such changes occur over a period of several weeks and may persist for months. They are often confused with scurvy and atypical dyschondroplasia. They differ from the former in being confined to one bone or in random distribution without involving the metaphyses. Years ago such cortical thickenings were usually mistaken for the results of syphilitic periosteitis.

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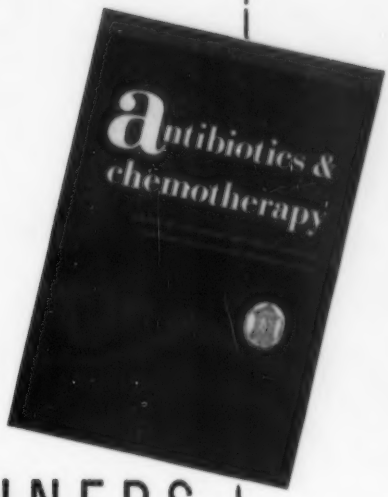

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